Remarks

Claim listing

Claims 1-20 and 24-31 are pending in the application. No amendments are made at this time.

Claim rejections under 35 U.S.C. §103

Claims 1-20 and 24-31 remain rejected as obvious over previously cited Sheng-Hui, (WO 97/43451), in view of DeClercq (U.S. 5,607,922) and Alexander (U.S. 5,659,023), also previously cited. The rejections are respectfully traversed.

The rejections are based on allegations of equivalency between compounds disclosed in separate references. The response is accompanied by a declaration of the inventor in rebuttal of the obviousness rejection. The declaration is in accordance with MPEP 2145 and 716.01(c)(II), to the extent that it presents scientific basis for complete lack of equivalency between the prior art compounds and points out different uses disclosed for the prior art compounds. The declaration also presents facts supporting the assertion that the combination of the prior art compounds would not have been made by a person of ordinary skill at the time of the invention.

The final rejection alleged that there is structural similarity between the compounds of Sheng-Hui and DeClercq. Furthermore, the final rejection alleged that "the prior art recognized use of the disclosed compounds in the same method as set forth in the instant claims, namely the synthesis of oligonucleotides." Therefore, "it would have been obvious to the ordinary skilled artisan to modify the reagents of Sheng-Hui with the substituted cyclohexene compounds of De Clercq."

i. De Clercq teaches a different compound from Sheng-Hui

It appears that the allegations of similarity between the prior art and the claimed compounds stem from the use of six-atom cyclical moieties. It is important to clarify that De Clercq moiety is NOT a substituted version of the Sheng-Hui moiety as alleged in the office action, but a compound from a different category. Sheng-Hui teaches cyclohexane, a saturated cycloalkane[1], which is a ring structure with an all-carbon ring. De Clercq does not teach cyclohexane or "substituted cyclohexene" as stated in the office action. Instead, De Clercq teaches substituted 1,5-anhydrohexitol, a cyclical alkyl ether, which is a ring structure containing an oxygen atom (col. 1, line 51). Furthermore, Sheng-Hui's cyclohexyl compounds do not contain a nucleobase. These compounds are not

[1] Sheng-Hui states: "X1 is a substituted or unsubstituted C5 to C7 cyclic moiety." (p. 7, line 22). "Commonly, X1 will be substituted or unsubstituted cyclohexane." (P. 8, lines 1-2).

nucleosides. On the other hand, De Clerq describes nucleoside analogs containing a nucleobase moiety.

ii. Prior art does NOT teach equivalence of compounds

MPEP 2144.06(II) states that "In order to rely on equivalence as a rationale supporting an obviousness rejection, the ***equivalency must be recognized in the prior art***, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." In the case of Sheng-Hui and De Clercq compounds, nothing in the cited prior art recognizes or suggests equivalency.

Sheng-Hui does not discuss alkyl ethers, but only cycloalkanes C5-C7 for the group X1. De Clercq does not suggest that 1,5-anhydrohexitol can be an equivalent to cycloalkanes in nucleotide analogs. De Clercq compares a single compound, 1,5-anhydro-hexitol to one other compound, pentofuranose, and only with respect to antiviral properties (col. 2, lines 54-60). Therefore nothing in the cited prior art suggests that 1,5-anhydrohexitol (or any form of hexitol) can be substituted for cyclohexane (or any cycloalkane) in nucleotides or nucleotide polymers.

On the chemical equivalence between cyclohexane and anhydrohexitol, the inventor has stated that they are not homologous. (See Decl., par. 8.) The inventor pointed out an additional critical difference: in Sheng-Hui's cyclohexane-based compounds, the functional groups necessary for chain elongation and oligonucleotide synthesis are connected to the same ring carbon, while in hexitol derivatives (such as De Clercq's or applicants' compounds) they are connected to different ring carbons. (See id.) Sheng-Hui does not state or suggest to link the two functional moieties to two different ring carbon atoms. The inventor concluded that "a skilled chemist would not substitute one for another." (See id.)

Based on the foregoing, the compounds of Sheng-Hui and De Clercq are NOT structural equivalents as alleged in the office action, and have not been recognized as such in the art.

iii. The compounds are NOT used for the same purpose

MPEP 2144.07 requires that "***the art recognize the suitability of the equivalents for the intended purpose.***" In the case of Sheng-Hui and De Clercq compounds, nothing in the prior art suggests use for the same purpose.

The purpose of the Sheng-Hui compounds is to synthesize a labeled nucleic acid *in vitro*. The purpose of De Clercq is to administer a single nucleoside to a virus in order to block replication of the virus. Neither reference mentions or suggests that antiviral

nucleosides are suitable for incorporation into nucleic acids in general or labeled oligonucleotides in particular. In fact, many antiviral compounds actually block nucleic acid synthesis.

On the different purposes of compounds in Sheng-Hui and De Clercq, the inventor has stated that Sheng-Hui describes labeling reagents for synthesis of labeled nucleic acids, which reagents do not contain a nucleobase. (See Decl. par. 9) De Clercq describes nucleosides and nucleotides with a nucleobase, which are different from the compounds of Sheng-Hui. (See id.) Further, the compounds of De Clercq are used only as monomers (i.e. are not incorporated into any nucleic acids) and are used only as antiviral agents. (See id.) In De Clercq, the inventor found "no guidance on how to obtain labeling reagents for oligonucleotide synthesis." (See id.)

Based on the foregoing, the compounds of Sheng-Hui and De Clercq have NOT been used for the same purpose, and have not been recognized as usable for the same purpose in the art.

iv. There is no reasonable expectation of similar properties

The office action alleged that the compounds of Sheng-Hui and De Clercq have "structural similarity," and stated generally that "homologs often have similar properties." However, MPEP 2144.09 states that "The presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is ***no reasonable expectation of similar properties*** in structurally similar compounds."

Sheng-Hui does not state or suggest that a saturated cycloalkane can be replaced with a different type of compound, specifically with an alkyl ether such as 1,5-anhydro-hexitol. The only contemplated variation in Sheng-Hui is among different cycloalkanes (C5, C6 or C7). De Clercq does not discuss any variations of the ring structure, but compares 1,5 anhydrohexitol to one other drug containing pentofuranosyl to find different anti-viral properties.

On the expectation of similar properties of cyclohexane and hexitol-containing nucleotides, the inventor has stated that at least three properties are essential for a nucleotide used in synthesis of a labeled oligonucleotide: 1) successful synthesis of a monomer; 2) incorporation [of the monomer] into an oligonucleotide; and 3) that the resulting oligonucleotide works as a probe, i.e. in a detection assay such as Taqman assay. (See Decl. par. 7). The inventor noted that DeClercq described only antiviral properties and nothing else, thus omitting properties "of enormous importance." (See id.) The inventor added that the necessary features omitted from De Clercq "were neither obvious

not foreseeable since 1,1-bis-hydroxymethyl-cyclohexane (the Sheng-Hui moiety) and 1,5-anhydrohexitol (the De Clercq moiety) are structurally different." (See id.)

v. Impermissible hindsight

MPEP 2145(X)(A) proscribes the use of hindsight, by defining as "impermissible" any reasoning that "includes knowledge gleaned ***only from applicant's disclosure.***" In fact, such impermissible hindsight reasoning has been applied in the latest office action.

As explained above, prior art does not recognize the compounds of Sheng-Hui and De Clercq as structurally equivalent or usable for the same purpose. De Clercq describes one of a myriad of antiviral compounds. The De Clercq's compound happens to contain a hexitol derivative. The inventor has stated that "there is a ***huge number*** of nucleoside analogs described in the art where the ribose sugar moiety has been modified or displaced by other structures. These nucleoside analogs in the monomeric form are tested as antiviral or anticancer agents." (See Decl. par 7). Prior art gives no clues why the antiviral nucleosides of De Clercq should be the ones singled out for a different application. The De Clercq reference itself provides no guidance on using the described compounds for the applicants' purposes. (See Decl. par. 10). The inventor has stated that "in hindsight, this choice [of compounds] turned out to be successful. However, the success could not have been predicted based on the knowledge in the art at the time." (See id.).

Therefore it is ***only the applicants' disclosure*** that describes or suggests successful use of hexitol-derived nucleotides in oligonucleotide synthesis. Using applicants' disclosure as the only evidence of obviousness is impermissible hindsight within the meaning of MPEP 2145(X)(A).

Based on the foregoing, the obviousness rejection of claims 1-20 and 24-31 may not be maintained. Withdrawal of the rejection is respectfully requested.

Conclusion:

It is believed that all claims are now in condition for allowance. It is also believed that no fee is due at this time, however, the Commissioner is hereby authorized to charge any fee deficiency, or credit any overpayment to Deposit Account No. 50-0812.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please call the undersigned directly at the number below.

Respectfully submitted,

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